

## DYSOVULATION\*

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RECENT advances in the knowledge of the physiology of menstruation have made possible the correlation of certain clinical symptoms with pathologic states not always attributed to disturbances of ovarian function. This is exemplified by a symptom complex to which the term "dysovulation" may be applied.

Dysovulation may be defined as difficulty in the normal physiological extrusion of the matured ovum from its Graafian follicle, and may lead to such pathological destinies as intermenstrual pain, cystic ovaries, ruptured Graafian follicle, and corpus luteum cysts and hyperestrus, with its accompanying emotional imbalance. An analysis of a series of twenty-two cases of dysovulation has brought to light the fact that a characteristic syndrome exists.

With the exception of two patients (Cases 2 and 42) each of the women in this series was seen first because of acute abdominal pain. The pain generally originated in the right lower quadrant. It appeared suddenly, was severe, persistent, and cramp-like in character. Usually, it was intense for the first day, and then gradually lessened. After the subsidence of the pain, there was sometimes a persistent burning sensation in the right side. With the pain, the patient was often nauseated, but vomiting never occurred. These patients also exhibited marked anxiety, nervousness, and irritability, or mental inactivity and muscular exhaustion. Occasionally tumors of the hands and feet were so marked as to dominate the picture. In two instances (Cases 38 and 43) generalized trembling and tachycardia accompanied the attack, and was so alarming that emergency medical aid was summoned.

Heart palpitation was a common symptom. Some of the patients complained of dizziness. Not infrequently there was moderate sweating during the attack, so that the statement was often made that "when I get the pain, my hands and feet become cold and clammy."

The invariable presence of these autonomic disturbances<sup>9,10</sup> should recall to the clinician the interdependence of the ovaries and the autonomic nervous system. Close questioning always brought to light the information that attacks of nervousness had recurred more or less regularly during the intermenstrum, and might last a day or two. The periodicity of the psychic upsets was another factor in focusing attention on the gonads as the seat of the pathology.

The arresting feature of the illness, and the most valuable diagnostic essential, is the time in the menstrual cycle when the symptoms arise. A thorough history elicited the fact that the attack of pain happened either during or immediately after the time of ovulation, which is approxi-

mately fourteen days after the onset of menstruation. Furthermore, in most cases, there was a story of repeated previous attacks. Some of the patients had suffered over a period of years, others for only a few months, while two (Cases 40 and 27) were operated on in the first attack. Other patients had experienced repeated episodes of unaccountable nervousness, which had recurred regularly in the intermenstrum and were associated with vague abdominal symptoms such as women often consider premonitory of menstruation.

When pain was the cardinal feature of the intermenstrual disturbances, the ensuing menstrual period was generally delayed. Such delay was usually of only a few days' duration; at other times there was a delay of weeks, even occasioning a suspicion of pregnancy. Five patients (Cases 146, 27, 20, 9, 85, and 2) not desirous of pregnancy, had had abortions performed; but a subsequent review of their histories indicated that the diagnosis of pregnancy had been entirely unsupported.

The general physical examination during the acute attack revealed no abnormality except the local findings in the abdomen. In one instance (Case 82) a massive intra-abdominal hemorrhage gave a picture of shock and internal hemorrhage. In the remaining patients no true rigidity was present in spite of the fact that the majority of the patients in our limited series gave a clinical history of localized right-sided lower abdominal pain at the onset of the illness. At operation the pathology was not necessarily limited to the right side. In two cases the pathology was entirely left-sided. A sufficient number of these cases has not yet been treated surgically to permit speculation on this almost uniform localization of pain to the right side.

With a history, such as we have described, particular stress was naturally laid on the pelvic examination, and only twice (Cases 2 and 11) was any abnormality palpable. All of these patients had been seen by gynecologists and, except for tenderness in the fornices, no gross lesion was reported. Blood pressure determinations gave low manometric readings in all instances. Of the other routine procedures, such as blood Wassermann, urinalysis, and basal metabolic rate, no information of diagnostic value was gained.

During the attack there was often an elevation of the white blood count with a high percentage of polymorphonuclear cells. We have seen the blood count change very rapidly, and return to within normal limits in as short a time as twenty-four hours. A low-grade temperature usually accompanied the attack. Two of the patients (Cases 129 and 146) who were desirous of becoming pregnant had a Rubin test, and one had an hysterosalpingography with lipiodol (Case 27) which showed patent tubes. Nevertheless, it is interesting to note that in none of these patients had a pregnancy occurred after the onset of the symptoms.

Six of the patients had consulted gynecologists regarding their sterility, but were advised that there was no demonstrable reason why pregnancy should not occur.

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## PATHOLOGIC CHANGES

An opportunity to establish the pathology responsible for the clinical picture was afforded in thirteen cases by operation. A large hemorrhagic excrescence was noted on the surface of the ovary in all the cases, and free blood in varying amounts was found in the peritoneal cavity. Both ovaries were somewhat enlarged; the surface was smooth and of milky-white color, and was the seat of numerous follicular cysts. In most instances there were adhesions to adjacent structures, and twice small inflammatory cysts on the tubes and broad ligament were seen. Four patients showed some thin adhesions to the meso-appendix, and the appendix was bound down by tenuous adhesions to the right ovary. Histologic study failed to reveal any acute inflammatory process in the appendices removed at operation.

## TREATMENT

Although the tendency in therapy is toward conservatism, nevertheless there are certain definite indications for operation. This indication is entirely dependent upon the severity of the intra-abdominal hemorrhage or persisting hemorrhage, which is determined by the general condition of the patient, the pulse rate, the blood pressure, hemoglobin determinations, and the degree of shock that is present. The operative procedure can only be determined upon visualization of the lesion. If there is any question of doubt as to the diagnosis, exploratory operation should be performed to obviate the danger of overlooking an acute appendicitis.

Conservative treatment is based on the theory that many of the symptoms that these patients complain of, particularly the nervous symptoms, are due to the hormonal imbalance produced by the local pathology. Blood and urine hormonal studies were, therefore, made in an attempt to determine the type of ovarian dyscrasia responsible for the condition. These studies showed a hyperestremia in most of the cases. Various hormonal preparations were tried therapeutically. Although it is too early to evaluate the results obtained with conservative treatment, nevertheless our limited experience seems to indicate that the symptomatic improvement is only transitory, as there have been four instances (Cases 92, 27, 11, and 43) of recurrence of symptoms at varying intervals after cessation of therapy.

## RECONSTRUCTION OF PROCESSES INVOLVED

It is interesting to attempt to reconstruct the processes involved. Granted a normal organic equipment, the maturation and discharge of the ovum from the ovary occurs on approximately the fourteenth day after the onset of the previous menstrual period.<sup>1, 2, 3, 6, 7</sup> When the ovarian tunic has become thickened from any cause whatsoever, there may be a hindrance to this normal physiological escape of the ovum. The Graafian follicle does not rupture, and there results an increase of the transudate, with the formation of a cyst. Some of the subsequent Graafian follicles may ultimately meet the same fate, producing multiple retention cysts. Thus we encounter cystic ovaries as one of the manifestations of "dysovulation."

At times an excessive amount of transudate is poured into the unruptured Graafian follicle. This may suddenly increase the tension so as to cause the rupture of the newly formed follicular cyst through the capsule of the ovary. If rupture of the follicular cyst does not occur, luteinization may proceed even in the presence of the increasing transudate. Finally, the tension may be sufficient to cause a late rupture of the distended follicular cyst. Thus, ruptured follicular or corpus luteum cysts present a second clinical manifestation of dysovulation. The rupture of the cysts which have reached the stage of luteinization is associated with considerably greater hemorrhage than occurs in the earlier stage. The severity of the clinical picture which these accidents give rise to depends entirely on the size of the associated intra-abdominal hemorrhage.

On the other hand, even in those cases of dysovulation where rupture of the cyst has not occurred, an acute abdominal syndrome may result from an acute distention of the Graafian follicle which so closely simulates appendicitis that exploratory laparotomy is done. Although at operation no other lesion than cystic ovaries is found, the symptomatology which provoked the surgery is rarely blamed on the ovaries, and a normal appendix is removed. Unfortunately, in such cases, intermenstrual pain is only infrequently recalled as a clinical entity. "Intermenstrual pain," first described by Priestly, fits only one symptom of dysovulation, and is therefore inadequate as a diagnosis. The Germans later rediscovered the syndrome and rechristened it "Mittelschmerz." All this antedated the experimental determination of the precise time of ovulation in the menstrual cycle. Consequently, there was no way of correlating the physiological event of ovulation and the pathological disturbance giving rise to the intermenstrual pain.

Most authors, according to Kauffman,<sup>12</sup> believe that there is an inflammatory exudative process concerned in the formation of follicular cysts because of the adhesions found in the neighborhood of the ovary. Our operative findings seemed to corroborate this viewpoint. The most recently offered explanations for the etiology of intermenstrual pain is that a chemical peritonitis is caused by the discharge of the follicular contents into the peritoneal cavity.<sup>7</sup> However, from observations at operation, it was evident that the severity of the abdominal symptoms was entirely dependent on the amount of blood extravasated into the peritoneum when rupture of the follicular cyst has finally occurred.

An excellent illustration of the probable mechanism responsible for the acute abdominal picture encountered was afforded in a patient (Case 62) who was being treated with daily injections of Collip's APL to control intermenstrual nervousness. After the patient had received three injections, there was an acute attack of abdominal pain with high temperature, and signs indicative of peritonitis. Operation was immediately performed; the site of a ruptured follicular cyst was seen in the right ovary; there was a large amount

of free blood in the abdominal cavity, and both ovaries were the seat of multiple cysts.

Collip and others<sup>13,14</sup> have demonstrated that follicular cysts may contain as much as 25 RU of estrin per cubic centimeter. In long-standing cases this excess of estrin leads to a marked hypertrophy of the endometrium of the uterus, as was demonstrated in three cases which we curetted for diagnostic purposes. The presence of multiple cysts is responsible for the continuous absorption into the circulation of large amounts of estrin, which not only influences the endometrium of the uterus, but affects the entire human organism by producing a more or less constant state of estrus with its accompanying emotional imbalance. Might this endocrine disturbance not account for many of the psychoneurosis met with in women?

Recently certain authors have claimed that a continuous hyperestrus results in uterine fibroids. Support for this theory was forthcoming by the finding of small uterine fibroids at operation in four of our cases, and it is also noteworthy that all four were young women.

The literature emphasizes the similarity of the clinical picture caused by ruptured ovarian cysts (follicle or corpus luteum) to acute or chronic appendicitis.<sup>8,17,22</sup> The obvious reason for the resemblance is that the seat of the pathology being in close proximity to the appendix, gives rise to an acute abdominal picture which may very closely simulate appendicitis. Furthermore, there are no essential differences in the physical findings in the two conditions, unless a massive intra-abdominal hemorrhage has occurred. Therefore, the clinician must rely on the history for the differential diagnosis.

#### SUMMARY

The pathogenesis of dysovulation, as reconstructed from pathological findings at operation, seems to justify the theory that various gynecological entities are the result of one common disturbance in the menstrual cycle.

The clinical syndrome of dysovulation is characterized by the regular periodic recurrence of attacks of autonomic imbalance, with occasional acute abdominal manifestations. These attacks always occur in the menstrual intermission at the anticipated time of ovulation. They can be attributed to an interference with this process. The literature<sup>8,16,17,18,19,20,21,22,28</sup> contains many case reports of ruptured corpus luteum cysts with massive intra-abdominal hemorrhage which is a complication of dysovulation.

The relative frequency with which the picture arising from dysovulation is confused with appendicitis is demonstrated by the fact that nineteen of the twenty-two cases reported here were sent to the surgeon for appendectomy.

The chronology of the symptoms which start exactly at the time of ovulation, and the history of repeated similar attacks in the past, following which the ensuing menstrual period has been delayed, should make possible a diagnosis of dysovulation. Such conditions as cystic ovaries, ruptured follicular or corpus luteum cysts and attacks of

intermenstrual nervousness should be considered as complications or manifestations of dysovulation.

There is also a possibility that hyperestremia, as one of the results of dysovulation, is the basis of many cases of psychoneurosis in women.

Lately it has been demonstrated that there is a definite association between hyperestremia, hyperplastic endometritis, and uterine fibroids.

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## DISCUSSION

ROLAND CUMMINGS, M. D. (523 West Sixth Street, Los Angeles).—In every case of a suspected appendicitis, the clinician has had to consider the possibility of the symptoms resulting from ovarian disease, and many times he concludes that the ovary is at fault regardless of his inability to explain the pathology.

It is interesting, therefore, to read the description of the disease under consideration written almost seventy years ago by Doctor Priestly. His outline of the symptomatology is very complete, and his observation of left-sided pain and tenderness much more common than has been observed by Doctor Hirshfeld. His theory of the ovarian changes during the monthly cycle were very shrewd when compared to the complete knowledge of the cycle existing today.

Rhodenburg and Hellman were able to produce cystic degeneration of the ovaries by injecting corpus luteum. Is it possible, then, that for some unknown reason there has been the production of an excessive amount of corpus luteum in the patients previous to the development of the cysts?

The point in the history regarding the time of the monthly cycle in which this trouble occurs emphasized by the author I wish to reemphasize, as the diagnosis will often hinge upon the correctness of this information.

I feel grateful to Doctor Hirshfeld for his clear delineation of the mechanism of the production of the symptoms due to dysovulation.

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ROY E. THOMAS, M. D. (1136 West Sixth Street, Los Angeles).—To the internist the chief interest of Doctor Hirshfeld's paper lies in those points which aid in the differential diagnosis between the accident described and acute appendicitis.

In the male the diagnosis of acute appendicitis rarely offers much difficulty; but in the female, after puberty, such a diagnosis is often a real problem. Among the more common conditions to be ruled out are acute salpingitis, extra-uterine pregnancy, and ruptured Graafian follicle or corpus luteum cyst. If the diagnosis of rupture of a Graafian follicle can be established with reasonable certainty, the patient is spared an unnecessary laparotomy.

Of first importance in the differential diagnosis of ruptured Graafian follicle simulating appendicitis is an accurate history. One or more previous attacks, of short duration, the absence of previous dyspepsia, the onset of pain in the lower abdomen rather than the epigastrium, and occurring approximately fourteen days after the beginning of the previous menstrual period, are against appendicitis as a cause of the attack.

On examination, the patient with a ruptured follicle is apt to be in a disturbed emotional state, presenting evidence of the autonomic upset described by Doctor Hirshfeld. Palpation of the abdomen shows less muscle spasm than is usually found in appendicitis. Why the pain is usually referred to the right lower quadrant when the pathology may be in either ovary, I cannot say.

Inasmuch as serious bleeding rarely occurs except with the rupture of a corpus luteum cyst (which comprised less than 20 per cent of Doctor Hirshfeld's series), it would seem that whenever the diagnosis seems reasonably certain, these cases should be treated conservatively, unless definite signs of progressive hemorrhage are present.

Dysovulation should be considered as a possible factor in the etiology of many functional disturbances in the female, and certainly in all cases presenting acute lower abdominal pain as a prominent symptom. Doctor Hirshfeld's paper is a timely one.

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FRED S. MODERN, M. D. (1135 Pacific Mutual Building, Los Angeles).—Dysovulation is a syndrome which has been known under various names, such as

"intermenstrual pain" and "Mittelschmerz," for some sixty-odd years; but Doctor Hirshfeld's paper is, to my knowledge, the first which adequately summarizes and discusses the condition. It must be a comparatively frequent condition, as the author collected twenty-two cases from his own private practice. It must also undoubtedly be frequently overlooked because its symptoms overlap with other more common abdominal disorders from which it is difficult to distinguish, the diagnosis depending on a careful history rather than on the physical findings during an attack.

Dysovulation is essentially a disorder of follicular rupture during ovulation. Symptoms may occur through failure of the follicle to discharge the ovum, and the increase of tension within the follicle due to an increased amount of follicular fluid. Hyperestremia and hyperluteinization may occur as a consequence with their ensuing train of autonomic symptoms due to the excess estrin production and delayed menstruation, or even amenorrhea may follow due to a persistent corpus luteum, if the follicles should fail to involute poly (micro) cystic ovaries may result. If, however, follicular rupture does occur, dependent on the stage of follicular development, we have the picture of an acute abdominal episode either due to a chemical peritonitis or to a more or less extensive intra-abdominal hemorrhage.

Therapeutically the problem is discouraging. Doctor Hirshfeld points out that he has attempted to treat four patients conservatively with opotherapy, all of whom relapsed. The acute attacks associated with true intraperitoneal complications have, as a matter of course, to be treated operatively, unfortunately without definite hope of an ultimate recovery unless mutilated by an oöphorectomy. My own personal experience extends only to a total of five cases of intermenstrual pain which could be tentatively interpreted as dysovulation. In three of the cases the condition was associated with a lowered basal rate and other symptoms indicating myxedema. These three cases responded brilliantly to the administration of thyroid extract and emmenin, the oral anterior pituitary-like preparation developed by Collipp. The other two cases had a normal basal rate and organotherapeutic treatment proved a flat failure.

The recent development of potent endocrine preparations has placed a powerful weapon at the disposal of the medical profession for good or bad. Experience is still lacking as to what side effects some of these preparations might have in long-continued use. Potent estrin-like extracts have been proved, at least in animal experimentation, to have a sclerosing effect on the ovary and its fibrous tunic. It stands to reason that dysovulation might be an undesired side effect, at times, of previous treatment with an estrin-like substance.

## BRUCELLA ABORTUS AGGLUTININS\*

A STUDY OF THEIR INCIDENCE IN THE BLOOD OF  
THE GENERAL POPULATION OF A CITY  
AND SEVERAL RURAL COMMUNITIES  
IN CALIFORNIA

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THE following is a report of a comparative study of the frequency of occurrence of *Brucella abortus* agglutinins in the blood of human beings, collected from the general population of a large urban community and from three rural communities in California. The urban group consisted of patients who registered in the out-patient clinics, and the wards of Lane and Stanford hospitals in

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